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(54) Title: ORAL PHARMACEUTICAL COMBINATIONS OF NSAIDS WITH TERPENOIDS

(57) Abstract

Pharmaceutical compositions for oral administration comprising an NSAID and a terpenoid compound are disclosed. They are useful in the treatment of inter alia painful conditions, pyretic conditions (fever) and inflammatory conditions. Furthermore, the invention concerns a method of treating inter alia painful conditions, pyretic conditions and inflammatory conditions which method comprises orally administering to a mammal including man a therapeutically effective amount of an NSAID together with a therapeutically effective amount of a terpenoid compound. Further the invention relates to the use of an NSAID compound together with a terpenoid compound (for the manufacture of a pharmaceutical composition adapted to oral administration) for the treatment of painful conditions, pyretic conditions and inflammatory conditions.

ORAL PHARMACEUTICAL COMBINATIONS OF NSAIDS WITH TERPENOIDS

The invention relates to the oral treatment of painful conditions, pyretic conditions (fever) and inflammatory conditions with non-steroidal antiinflammatory drugs (NSAIDs) as well as to novel pharmaceutical compositions adapted to oral administration comprising NSAIDs.

The oral administration of NSAIDs as analgesics, anti-pyretic drugs or anti-inflammatory drugs is known in the art.

It has now surprisingly been found that by combining an NSAID with a terpenoid compound in a pharmaceutical composition for oral administration the analgesic, anti-pyretic and anti-inflammatory efficacy of the combination is enhanced in an unexpected manner. Moreover, the combinations of the invention show, unexpectedly, a very much improved side effect profile, i.e. the adverse effects typical for orally administered NSAIDs, such as gastric irritation, gastric ulceration, gastric bleeding, nephrotoxicity, acute renal failure, jaundice, nausea, dyspepsia, peripheral edema, rash, pruritus, tinnitus, dizziness, headache, anxiety, aseptic meningitis or fluid retention, can only be detected to a far lesser extent than with NSAID monotherapy alone.

Therefore, the invention relates to the use of a non-steroidal antiinflammatory drug in combination with a terpenoid compound (for the manufacture of a medicament adapted to oral administration) for the treatment of painful conditions, pyretic conditions or inflammatory conditions.

Painful conditions, pyretic conditions or inflammatory conditions are, for example: musculoskeletal disorders such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis; acute gouty arthritis; rheumatic fever; fever; dysmenorrhea; inflammatory bowel disease, Morbus Crohn, colitis ulcerosa; migraine (prevention or treatment); acute musculoskeletal pain; muscle strain; headache, e.g. tension-type headache, toothache, muscular pain (myalgia, strain), back pain, shoulder pain, bursitis, tendinitis or epicondylitis.

A non-steroidal antiinflammatory drug is, for example, salicylic acid or a derivative thereof, e.g. acetaminosalol, benorylate, bromosaligenin; aspirin (= acetylsalicylic acid) or a

pharmaceutically acceptable salt thereof, e.g. calcium acetylsalicylate or lysine acetylsalicylate; diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide O-acetic acid, salicylsulfuric acid, salsalate or sulfasalazine; an aminoarylcarboxylic acid or a derivative thereof, e.g. enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate or tolfenamic acid; an (aryl or heteroaryl)-alkylcarboxylic acid or a derivative thereof, such as acemetacin, alclofenac, amfenac, bufexamac, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclofenac, fenclorac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, zomepirac, bumadizon, butifen, fenbufen, xenbucin, clidanac, ketorolac, tinoridine, alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, miroprofen, naproxen, oxaprozin, piketoprofen, pirprofen, pranaprofen, protizinic acid, suprofen or tiaprofenic acid; a thiazinecarboxamide, e.g. droxicam, isoxicam, piroxicam or tenoxicam; a pyrazole derivative, e.g. difenamizole or epirizole; a pyrazolone derivative, e.g. apazone, benzpiperylon, febrazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone or thiazolinobutazone; or a non-steroidal antiinflammatory drug of another structure, e.g. epsilon-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole or tenidap; or a pharmaceutically acceptable salt thereof.

Preferred NSAIDs are aspirin, especially aspirin, calcium acetylsalicylate or lysine acetylsalicylate; salicylic acid, acetaminophen; diclofenac, especially diclofenac, diclofenac sodium or diclofenac potassium; diflunisal, etodolac; fenoprofen, especially fenoprofen or fenoprofen calcium; flurbiprofen; ibuprofen, especially S-ibuprofen; indomethacin, ketoprofen, ketorolac; meclofenamic acid, especially meclofenamic acid or meclofenate sodium monohydrate; mefenamic acid, nabumetone; naproxen, especially naproxen or naproxen sodium; oxaprozin, phenylbutazone, piroxicam, sulindac and tolmetin, especially tolmetin or tolmetin sodium; and pharmaceutically acceptable salts thereof.

Particularly preferred NSAIDs are ibuprofen, especially S-ibuprofen, ketoprofen, diclofenac and aspirin, and pharmaceutically acceptable salts thereof. First and foremost preferred are S-ibuprofen, diclofenac and aspirin, and pharmaceutically acceptable salts thereof.

A pharmaceutically acceptable salt of an NSAID having an acidic group is e.g. an alkali metal or alkaline earth metal salt, e.g. the sodium, potassium, magnesium or calcium salt, an aluminium salt or a transition metal salt, e.g. the zinc or copper salt, or a corresponding salt with ammonia or organic amines. Organic amines that come into consideration are, for example, the following: alkylamines, such as mono-, di- or tri-lower alkylamines, e.g. ethylamine, tert-butylamine, diethylamine, diisopropylamine, trimethylamine or triethylamine, alkylenediamines, such as lower alkylenediamines, e.g. ethylenediamine, alkylamines substituted by phenyl, such as mono- or di-phenyl-lower alkylamines, e.g. benzylamine or 1- or 2-phenylethylamine, hydroxy-alkylamines, such as mono-, di- or tri-hydroxy-lower alkylamines, e.g. mono-, di- or tri-ethanolamine or diisopropanolamine, oligohydroxy-lower alkylamines, e.g. tris-(hydroxymethyl)-methylamine, hydroxy-lower alkyl-di-lower alkylamines, e.g. N,N-dimethylamino- or N,N-diethylamino-ethanol, amino sugars, such as those in which the amino group is optionally substituted by at least one lower alkyl group, e.g. D-glucosamine, D-galactosamine or marmosamine (derived from monosaccharides in which an alcoholic hydroxy group is replaced by an amino group) or N-methyl-D-glucosamine (an N-lower alkylated amino sugar), cycloalkylamines, such as mono- or di-cycloalkylamines, e.g. cyclohexylamine or dicyclohexylamine, basic amino acids, e.g. arginine, histidine, lysine or ornithine, or cyclic amines, such as lower alkyleneamines or lower alkenyleneamines, e.g. azirine, pyrrolidine, 1-ethyl-pyrrolidine, 2-hydroxyethyl-pyrrolidine, piperidine, 1-ethyl-piperidine, 2-hydroxyethyl-piperidine or pyrroline, or lower alkyleneamines or lower alkenyleneamines in which the carbon chain is interrupted by aza (-NH-), N-lower alkylaza [-N(-lower alkyl)-], oxa (-O-) and/or thia (-S-), e.g. imidazoline, 3-methylimidazoline, piperazine, 4-methyl- or 4-ethylpiperazine, morpholine or thiomorpholine.

A pharmaceutically acceptable salt of an NSAID having a basic group is e.g. an acid addition salt. Suitable acid components may be, for example, strong inorganic acids, typically mineral acids, e.g. sulfuric acid, phosphoric acids, e.g. orthophosphoric acid, hydrohalic acids, e.g. hydrochloric acid, or strong organic carboxylic acids, typically lower alkanecarboxylic acids which may be substituted, e.g. by halogen, such as acetic acid or

trifluoroacetic acid, dicarboxylic acids which may be unsaturated, e.g. oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, e.g. ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, e.g. aspartic or glutaminic acid, or benzoic acid, or organic sulfonic acids, typically lower alkanesulfonic acids which may be substituted, e.g. by halogen, typically methanesulfonic acid, or arylsulfonic acids which may be substituted, e.g. by lower alkyl, typically p-toluenesulfonic acid.

A terpenoid compound is, for example, a monoterpenoid compound, a diterpenoid compound, a triterpenoid compound or a sesquiterpenoid compound.

A monoterpenoid compound is e.g. camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, e.g. 1,8-cineol; gefarnate, geraniol, linalool, limonene, menthol, pulegone or thymol.

A diterpenoid compound is e.g. aphidicolin, forskolin, phytanic acid or phytol.

A triterpenoid compound is, for example, glycyrrhetinic acid or diosgenin.

A sesquiterpenoid compound is e.g. farnesol or santonin.

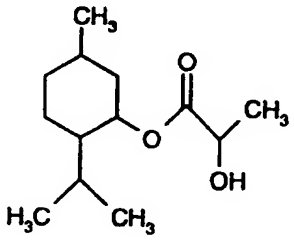
The term "terpenoid compound" is intended also to cover any derivative and any pharmaceutically acceptable salt of a terpenoid compound. Preferred derivatives of a terpenoid compound having one or more hydroxy groups are those wherein one or more of the hydroxy groups are esterified by a carboxylic acid (= terpenoid compound esters).

A carboxylic acid is, for example, a C_1-C_7-aliphatic, a cycloaliphatic, an aromatic, an aromatic-C_1-C_7-aliphatic, a heteroaromatic or a heteroaromatic-C_1-C_7-aliphatic carboxylic acid, which carboxylic acid may be unsubstituted or substituted, for example by one or more substituents selected from hydroxy, halogen, C_1-C_7-alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, cyano, amino, C_1-C_7-alkylamino, di-C_1-C_7-alkylamino, C_1-C_7-alkanoylamino, nitro, C_1-C_7-alkyl and halogen-C_1-C_7-alkyl (e.g.trifluoromethyl). More especially, a carboxylic acid is a C_1-C_7-alkanoic acid which is unsubstituted or substituted by hydroxy, halogen, carboxy or amino, a C_3-C_7-cycloalkanoic acid; a phenyl-C_1-C_7-alkanoic acid, a benzoic acid or a naphthoic acid in each of which the phenyl ring(s) may be unsubstituted or substituted by one or more

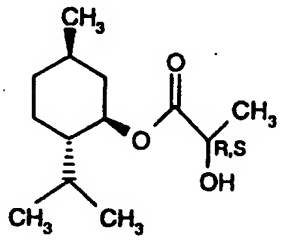
substituents selected from C_1-C_7-alkyl, halogen-C_1-C_7-alkyl, hydroxy, halogen, C_1-C_7-alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, cyano, amino, C_1-C_7-alkylamino, di-C_1-C_7-alkylamino, C_1-C_7-alkanoylamino and nitro; or a heteroaromatic carboxylic acid or a heteroaromatic-C_1-C_7-alkanoic acid in each of which the heteroaromate is selected from furan optionally substituted by C_1-C_7-alkyl or halogen, thiophene optionally substituted by C_1-C_7-alkyl or halogen and pyridine optionally substituted by hydroxy, lower alkoxy, trifluoromethyl, cyano or C_1-C_7-alkyl. In particular, a carboxylic acid is a C_1-C_7-alkanoic acid which is unsubstituted or substituted by hydroxy.

Preferred terpenoid compounds are menthol, menthol esters, especially menthyl lactate, or cineol, more preferably menthol or menthyl lactate, and in one embodiment menthol, and in another embodiment menthyl lactate.

The structural formula of menthyl lactate is as follows:



As the compound contains 4 asymmetric carbon atoms, there are existing 16 different stereoisomers. The term "menthyl lactate" is intended to cover each of these stereoisomers as well as any racemates and any other mixtures of these stereoisomers. Preferred is the racemate of the following structure



which is derived from the naturally occurring (-)-menthol. This compound is available commercially e.g. from Haarmann & Reimer GmbH (Germany) under the name FRESCOLAT, Type ML. It can also be readily made by processes known in the art by esterifiying the hydroxy group of menthol with lactic acid.

The oral pharmaceutical compositions of the invention have valuable pharmacological properties. Especially they are beneficial in the treatment of osteoarthritis, rheumatoid arthritis, acute musculoskeletal pain, dysmenorrhea, headache, toothache, fever, muscular pain, back pain, shoulder pain, bursitis, tendinitis or epicondylitis. The beneficial effects of the combinations are especially pronounced, when the terpenoid compound(s) is (are) applied in surprisingly high doses. It is believed that the terpenoid compounds act as powerful and specifically COX_2-inhibiting NSAIDs on their own and thus ideally complement the activity of usual NSAIDs (predominantly COX_1-inhibiting).

The beneficial properties of the combinations of the invention can be demonstrated, for example, in the following tests.

Reducing the carrageenin induced paw edema in the rat [see Winter C.A. et al., Proc. Soc. Exp. Biol. Med. 111 (1962) 544-547].

Lowering the pain threshold in yeast injected hindpaw in the rat [see L. Randall and J. Selitto, Arch. Int. Pharmacodyn. 111 (1957) 409-419].

Prevention of the development of adjuvant-induced arthritis in the rat [see C. Pearson et al., J. Exp. Med. 113 (1961) 485-509].

The reduction of NSAID-caused gastro-intestinal side effects can be demonstrated e.g. in a rodent model (rat) described in J. Pharmacol. Experi. Therapeutics 277 (1996) 1221-1227.

The oral pharmaceutical compositions obtainable by combining an NSAID with a terpenoid compound form a further object of the present invention.

Thus the invention further relates to a pharmaceutical composition adapted to oral administration comprising at least one NSAID and at least one terpenoid compound together with at least one pharmaceutically acceptable carrier.

Preferably, the pharmaceutical compositions according to the invention comprise both the NSAID(s) and the terpenoid compound(s) in pharmacologically effective amounts.

The dosage of the active ingredients may depend on various factors, such as warm-blooded species, sex, age, weight and individual condition of the warm-blooded animal.

Normally the daily dosage which is administered to a warm-blooded animal weighing approximately 75 kg is of from 0.1 up to 100 mg/kg, especially of from 0.15 up to 60 mg/kg, more especially of from 0.25 up to 55 mg/kg, of the NSAID and of from 0.1 up to 100 mg/kg, especially of from 0.3 up to 60 mg/kg, more especially of from 0.5 up to 55 mg/kg, most especially of from 1 up to 30 mg/kg and in particular of from 1.2 up to 20 mg/kg, of the terpenoid compound ("mg/kg" means mg drug per kg body weight of the mammal - including man - to be treated). These doses may be taken once daily or, if desired, also in several, optionally equal, partial doses.

The pharmaceutical compositions of the invention may be in single dose unit form or in non-single dose unit form. If in single dose unit form, they contain preferably of from 1% up to 90%, preferably of from 10% up to 50%, of the active ingredients (all percentages given are percentages by weight, if not indicated otherwise). Single dose unit forms such as capsules, tablets or dragées contain e.g. of from 10 up to 1000 mg, especially of from 20 up to 800 mg and in particular of from 50 up to 800 mg, of the active ingredients.

In single dose unit forms, the NSAID(s) is (are) e.g. present in an amount of from 1 up to 1200 mg, especially of from 5 up to 1000 mg and more especially of from 10 up to 800 mg.

When diclofenac, or a pharmaceutically acceptable salt thereof, is applied as NSAID in an oral single dose unit composition of the invention, the NSAID is preferably present in an amount of from 10 up to 200 mg, especially of from 10 up to 100 mg and more especially of from 20 up to 75 mg.

When ibuprofen or S-ibuprofen, or a pharmaceutically acceptable salt thereof, is applied as NSAID in an oral single dose unit composition of the invention, the NSAID is preferably present in an amount of from 20 up to 1000 mg, especially of from 50 up to 800 mg and more especially of from 75 up to 800 mg.

When aspirin, or a pharmaceutically acceptable salt thereof, is applied as NSAID in an oral single dose unit composition of the invention, the NSAID is preferably present in an amount of from 50 up to 1200 mg, especially of from 100 up to 1000 mg and more especially of from 250 up to 800 mg.

In single dose unit forms, the terpenoid compound(s) is (are) e.g. present in an amount of at least 1 mg, preferably in an amount of at least 10 mg, more preferably in an amount of at least 20 mg, even more preferably in an amount of at least 30 mg, most preferably in an amount of at least 50 mg, in particular in an amount of at least 80 mg, advantageously in an amount of at least 100 mg, more advantageously in an amount of at least 150 mg; and most advantageously in an amount of at least 200 mg; or in an amount of from 1 up to 1200 mg, especially of from 10 up to 1000 mg, more especially of from 20 up to 600 mg and first and foremost of from 50 up to 500 mg.

Pharmaceutical compositions for oral administration in single dose unit form are, for example, dragées, tablets or capsules. Moreover, sachets filled with the active substance in powder or granule form come into consideration. All these pharmaceutical compositions are prepared in a manner known per se, for example by means of conventional mixing, granulating or confectioning processes. For example, they can be obtained by combining the active ingredients with solid carriers, optionally granulating a resulting mixture and processing the mixture or granules, after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the

above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, e.g. solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, or polyacrylates, which means homo- or co-polymers of alkyl esters, especially methyl and ethyl esters but also e.g. substituted alkyl esters such as dimethylaminoethyl esters, of acrylic acid and/or methacrylic acid (and also of free acrylic acid and/or methacrylic acid), e.g. Eudragit® products such as Eudragit® S, Eudragit® NE, Eudragit® E or Eudragit® L (e.g. Eudragit® L30-D) of Roehm Pharma GmbH, Darmstadt (Germany). Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredients.

Other oral pharmaceutical compositions in single dose unit form are e.g. hard gelatin capsules made of gelatin, and soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredients in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules, the active ingredients are preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Pharmaceutical compositions in non-single dose unit form are, for example, syrups, liquid suspensions or solutions. They are prepared in customary manner. Typically, they contain the active ingredients in a concentration of from 0.1 up to 50%, preferably of from 0.1 up to 40%, more preferably of from 0.5 up to 30%, most preferably of from 1 to 20%, and especially of from 1 to 10%, or in a concentration that provides a suitable single dose when administered e.g. in a measure of 1, 5 or 10 ml.

In a non-single dose unit form, the NSAID(s) is (are) typically present in a concentration from 0.1% up to 50%, preferably of from 0.1% up to 20%, more preferably of from 0.5% up to 15%, most preferably of from 0.5 up to 10%, and especially of from 1 up to 10%.

In a non-single dose unit form, the terpenoid compound(s) is (are) typically present in a concentration of at least 0.5%, preferably at least 1%, more preferably at least 2%, especially in a concentration of from 0.1 up to 50%, more especially of from 0.5 up to 30%, most especially of from 1 up to 25%, advantageously of from 1 to 20%, and in particular of from 2 up to 10%.

Pharmaceutical compositions which are in enteric-coated form - and this especially concerns those in single dose unit form - form a preferred embodiment of the invention. Enteric-coated means that the coating is resistant to gastric juice but soluble in the small intestine where the active substances are released.

The following examples are intended to exemplify but not to limit the invention.

Example 1: Soft capsules: 5000 soft gelatin capsules, each comprising 50 mg of diclofenac sodium and 50 mg of menthyl lactate, are prepared as follows.

Composition (for 5 000 capsules)	
diclofenac sodium	250 g
menthyl lactate	250 g
Lauroglycol®	2 l

Preparation process: The diclofenac sodium and menthyl lactate are suspended in Lauroglycol® (= propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground to a particle size of approximately from 1 to 3 mm in a wet pulverizer. 500 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 2: Soft capsules: 5000 soft gelatin capsules, each comprising 50 mg of diclofenac sodium and 50 mg of menthyl lactate are prepared as follows.

Composition (for 5 000 capsules)

diclofenac sodium	250 g
menthyl lactate	250 g
PEG 400	1.8 l
Tween 80®	0.01 l

Preparation process: The diclofenac sodium and menthyl lactate are suspended in PEG 400 (= polyethylene glycol with M_r from approximately 380 to approximately 420, Fluka, Switzerland) and Tween 80® (= polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind., Inc., USA, supplied by Fluka, Switzerland) and is ground to a particle size of approximately from 1 to 3 mm in a wet pulverizer. 462 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 3: Dry-fill capsules: 5000 capsules, each comprising 50 mg of diclofenac sodium and 250 mg of menthyl lactate are prepared as follows.

Composition (for 5000 capsules)

diclofenac sodium	250 g
menthyl lactate	1250 g
talcum	100 g
magnesium stearate	20 g
mannitol	280 g

Preparation process: The powdered substances mentioned are pressed through a sieve having a mesh size of 0.6 mm. 380 mg portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.

Example 4: Hard gelatin capsules containing 25 mg diclofenac sodium of and 500 mg menthyl lactate are prepared as follows.

Composition (for 1000 capsules)

diclofenac sodium	25 g
menthyl lactate	500 g

microcrystalline cellulose	200 g
sodium lauryl sulfate	1 g
magnesium stearate	1 g

Preparation process: The diclofenac sodium, menthyl lactate, microcrystalline cellulose and sodium lauryl sulfate are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 727 mg portions of the resulting formulation are introduced into hard gelatin capsules of suitable size.

Example 5: Enteric-coated tablets containing 25 mg of diclofenac sodium and 250 mg of menthyl lactate are prepared as follows.

Composition (for 1000 capsules)

diclofenac sodium	25 g
menthyl lactate	250 g
microcrystalline cellulose	200 g
lactose	70 g
magnesium stearate	1 g
Eudragit® L30-D	20 g
polyethylene glycol	6 g
talc	10 g
distilled water	50 ml

Preparation process: The diclofenac sodium, menthyl lactate, microcrystalline cellulose and lactose are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 546 mg portions of the resulting formulation are pressed to biconvex tablets of 12 mm diameter size. For the coating solution, the polyethylene glycol is dissolved in water, then the talc is dispersed in this solution and the Eudragit® L30-D is added upon stirring. This solution is applied to the tablets by the means of a suitable coating equipment.

Example 6: Enteric-coated tablets containing 25 mg of diclofenac sodium and 250 mg of l-menthol are prepared as follows.

Composition (for 1000 capsules)

diclofenac sodium	25 g
l-menthol	250 g
microcrystalline cellulose	200 g
lactose	70 g
magnesium stearate	1 g
Eudragit® L30-D	20 g
polyethylene glycol	6 g
talc	10 g
distilled water	50 ml

Preparation process: The diclofenac sodium, l-menthol, microcrystalline cellulose and lactose are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 546 mg portions of the resulting formulation are pressed to biconvex tablets of 12 mm diameter size. For the coating solution, the polyethylene glycol is dissolved in water, then the talc is dispersed in this solution and the Eudragit® L30-D is added upon stirring. This solution is applied to the tablets by the means of a suitable coating equipment.

Claims

1. Use of an NSAID in combination with a terpenoid compound for the manufacture of a medicament adapted to oral administration for the treatment of painful conditions, pyretic conditions or inflammatory conditions.

2. Use according to claim 1, where the NSAID(s) is (are) selected from aspirin, salicylic acid, acetaminophen, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen; ibuprofen, S-ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac and tolmetin, and pharmaceutically acceptable salts thereof.

3. Use according to claim 1, where the NSAID(s) is (are) selected from ibuprofen, S-ibuprofen, ketoprofen, diclofenac and aspirin, and pharmaceutically acceptable salts thereof.

4. Use according to any one of claims 1 to 3, where the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, diosgenin, farnesol and santonin; wherein any hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof.

5. Use according to any one of claims 1 to 3, where the terpenoid compound(s) is (are) selected from menthol, menthol esters and cineol.

6. Use according to any one of claims 1 to 3, where the terpenoid compound(s) is (are) selected from menthol and menthyl lactate.

7. Use of an NSAID in combination with a terpenoid compound according to any one of claims 1 to 6,

where a pharmaceutical composition in single dose unit form is manufactured, in which the NSAID is present in an amount of from 5 up to 1000 mg and the terpenoid compound is present in an amount of at least 10 mg, or

where a pharmaceutical composition in non-single dose unit form is manufactured, in which the NSAID is present in a concentration from 0.5% up to 15% and the terpenoid compound is present in a concentration of at least 0.5% of the total composition.

8. Use of an NSAID in combination with a terpenoid compound according to any one of claims 1 to 7, where a pharmaceutical composition in single dose unit form is manufactured, in which the NSAID is present in an amount of from 10 up to 800 mg and the terpenoid compound is present in an amount of at least 30 mg.

9. Use according to any one of claims 1 to 8, where a medicament for the treatment of osteoarthritis, rheumatoid arthritis, acute musculoskeletal pain, dysmenorrhea, headache, toothache, fever, muscular pain, back pain, shoulder pain, bursitis, tendinitis or epicondylitis is manufactured.

10. A pharmaceutical composition adapted to oral administration comprising at least one NSAID and at least one terpenoid compound together with at least one pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10,

wherein the NSAID drug(s) is (are) selected from aspirin, salicylic acid, acetaminophen, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen; ibuprofen, S-ibuprofen, indomethacin, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac and tolmetin, and pharmaceutically acceptable salts thereof;

wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, diosgenin, farnesol and santonin; in which terpenoid compound any

hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof;

which pharmaceutical composition does not contain a local anaesthetic,

which pharmaceutical composition, if in single dose unit form, contains the NSAID(s) in an amount of from 10 up to 1000 mg and the terpenoid compound(s) in an amount of at least 10 mg, whereby the amount of the terpenoid compound(s) is less than 81% of the total composition;

which pharmaceutical composition, if in non-single dose unit form, contains the NSAID(s) in a concentration of from 0.5 up to 15% and the terpenoid compound(s) in a concentration of at least 0.3%;

in which pharmaceutical composition, if in single dose unit form and consisting of one or more cores that are coated, the terpenoid compound(s) is (are) present in the core(s) and may or may not be present in the coating.

12. A pharmaceutical composition according to claim 10, wherein the NSAID drug(s) is (are) selected from aspirin, salicylic acid, acetaminophen, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen; ibuprofen, S-ibuprofen, indomethacin, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac and tolmetin, and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition according to claim 10 or claim 11, wherein the NSAID drug(s) is (are) selected from ibuprofen, S-ibuprofen, diclofenac and aspirin, and pharmaceutically acceptable salts thereof.

14. A pharmaceutical composition according to any one of claims 10 or 12 to 13, wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, diosgenin, farnesol and santonin; in which terpenoid compound any

hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition according to any one of claims 10 to 13, where the terpenoid compound(s) is (are) selected from menthol, menthol esters and cineol.

16. A pharmaceutical composition according to any one of claims 10 to 13, where the terpenoid compound(s) is (are) selected from menthol and menthyl lactate.

17. A pharmaceutical composition according to any one of claims 10 to 16,

which is in single dose unit form, and in which the NSAID(s) is (are) present in an amount of from 5 up to 1000 mg and the terpenoid compound(s) is (are) present in an amount of at least 10 mg, or

which is in non-single dose unit form, and in which the NSAID(s) is (are) present in a concentration from 0.5% up to 15% and the terpenoid compound(s) is (are) present in a concentration of at least 0.5% of the total composition.

18. A pharmaceutical composition according to any one of claims 10 to 16, which is in single dose unit form, and in which the NSAID(s) is (are) present in an amount of from 10 up to 800 mg and the terpenoid compound(s) is (are) present in an amount of at least 30 mg.

19. A pharmaceutical composition according to any one of claims 10 to 18, which is in enteric-coated form.

20. A method of treating painful conditions, pyretic conditions or inflammatory conditions, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of an NSAID together with a therapeutically effective amount of a terpenoid compound.